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NEWS	6	Aug 26	Sequence searching in REGISTRY enhanced
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NEWS	8	Sep 16	Experimental properties added to the REGISTRY file
NEWS	9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
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NEWS	12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	13	Nov 18	DKILIT has been renamed APOLLIT
NEWS	14	Nov 25	More calculated properties added to REGISTRY
NEWS	15	Dec 04	CSA files on STN
NEWS	16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS	17	Dec 17	TOXCENTER enhanced with additional content
NEWS	18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS	20	Feb 13	CANCERLIT is no longer being updated
NEWS	21	Feb 24	METADEX enhancements
NEWS	22	Feb 24	PCTGEN now available on STN
NEWS	23	Feb 24	TEMA now available on STN
NEWS	24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS	25	Feb 26	PCTFULL now contains images
NEWS	26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS	27	Mar 20	EVENTLINE will be removed from STN
NEWS	28	Mar 24	PATDPAFULL now available on STN
NEWS	29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS	30	Apr 11	Display formats in DGENE enhanced
NEWS	31	Apr 14	MEDLINE Reload
NEWS	32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS	33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS	34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS	35	Apr 28	RDISCLOSURE now available on STN
NEWS	36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS	37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS	38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS	39	May 16	CHEMREACT will be removed from STN
NEWS	40	May 19	Simultaneous left and right truncation added to WSCA
NEWS	41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),

AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003

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=> s vanadium and sulfonylurea?

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=> file uspatfull

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FULL ESTIMATED COST	0.21	0.21

FILE 'USPATFULL' ENTERED AT 14:23:41 ON 20 MAY 2003

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 15 May 2003 (20030515/PD)

FILE LAST UPDATED: 15 May 2003 (20030515/ED)

HIGHEST GRANTED PATENT NUMBER: US6564383

HIGHEST APPLICATION PUBLICATION NUMBER: US2003093849

CA INDEXING IS CURRENT THROUGH 15 May 2003 (20030515/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 15 May 2003 (20030515/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

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>>> classifications, or claims, that may potentially change from <<<
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>>> the earliest to the latest publication.

<<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s canadum and sulfonylurea

21 CANADIUM

2209 SULFONYLUREA

L1 0 CANADIUM AND SULFONYLUREA

=> s vanadium and sulfonylurea

40027 VANADIUM

2209 SULFONYLUREA

L2 61 VANADIUM AND SULFONYLUREA

=> s vanadium and sulfonylurea?

40027 VANADIUM

3488 SULFONYLUREA?

L3 104 VANADIUM AND SULFONYLUREA?

=> s l3 and 10mg

609 10MG

L4 0 L3 AND 10MG

=> s l3 and 15mg

163 15MG

L5 0 L3 AND 15MG

=> s l3 and diabetes

24701 DIABETES

L6 100 L3 AND DIABETES

=> s l6 and mg

305571 MG

L7 95 L6 AND MG

=> s l7 and pd <1998

2268293 PD <1998

(PD<19980000)

L8 3 L7 AND PD <1998

=> d l8 1-3

L8 ANSWER 1 OF 3 USPATFULL

AN 2001:168152 USPATFULL

TI Substituted n-(indole-2-carbonyl-) amides and derivatives as glycogen phosphorylase inhibitors

IN Hulin, Bernard, Essex, CT, United States

Hoover, Dennis J., Stonington, CT, United States

Treadway, Judith L., Gales Ferry, CT, United States

Martin, William H., Essex, CT, United States

PA Pfizer Inc., New York, NY, United States (U.S. corporation)

PI US 6297269 B1 20011002

WO 9639385 19961212

AI US 1997-952668 19971202 (8)

WO 1995-IB443 19950606

19971202 PCT 371 date

19971202 PCT 102(e) date

DT Utility

FS GRANTED

LN.CNT 4318

INCL INCLM: 514/414.000

INCLS: 548/491.000; 548/492.000
NCLM: 514/414.000
NCLS: 548/491.000; 548/492.000
IC [7]
ICM: A01N043-38
ICS: C07D209-10; C07D209-42
EXF 548/492; 548/491; 548/414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 3 USPATFULL
AN 2000:109834 USPATFULL
TI Substituted n-(indole-2-carbonyl)-glycinamides and derivatives as
glycogen phosphorylase inhibitors
IN Hoover, Dennis J., Stonington, CT, United States
Hulin, Bernard, Essex, CT, United States
Martin, William H., Essex, CT, United States
Phillips, Douglas, Gales Ferry, CT, United States
Treadway, Judith L., Gales Ferry, CT, United States
PA Pfizer, Inc., New York, NY, United States (U.S. corporation)
PI US 6107329 20000822
WO 9639384 19961212 <--
AI US 1997-952669 19971202 (8)
WO 1995-IB442 19950606
19971202 PCT 371 date
19971202 PCT 102(e) date

DT Utility
FS Granted
LN.CNT 5662

INCL INCLM: 514/415.000
INCLS: 514/018.000; 514/419.000; 514/235.200; 514/323.000; 514/330.000;
514/385.000; 548/100.000
NCLM: 514/415.000
NCLS: 514/018.000; 514/235.200; 514/323.000; 514/330.000; 514/385.000;
514/419.000; 548/100.000

IC [7]
ICM: A01N043-38
ICS: A01N043-40; A01N043-52; A61K031-405
EXF 514/18; 514/415; 514/419; 514/235.2; 514/323; 514/330; 514/385; 548/100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 3 USPATFULL
AN 94:28742 USPATFULL
TI Complexed **vanadium** for the treatment of **diabetes**
mellitus
IN McNeill, John H., Delta, Canada
Hoveyda, Hamid R., Vancouver, Canada
Orvig, Chris, Vancouver, Canada
PA The University of British Columbia, Vancouver, Canada (non-U.S.
corporation)
PI US 5300496 19940405 <--
AI US 1991-767510 19910930 (7)
DT Utility
FS Granted
LN.CNT 459
INCL INCLM: 514/186.000
INCLS: 514/492.000; 514/884.000
NCLM: 514/186.000
NCLS: 514/492.000; 514/884.000
IC [5]
ICM: A61K031-555
ICS: A61K031-28
EXF 514/184; 514/186; 514/492; 514/884

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 181-3 kwic

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INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU
ALLG ----- ALL plus PAGE.DRAW
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PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, IN.CNT
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FP ----- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI,
PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL,
NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP,
CLMN, DRWN, AB
FP.EX ----- FP for original and latest publication
FPALL ----- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM,
NCLS, EXF, REP, REN, ARTU, EXNAM, LREP, CLMN, DRWN, AB,
PARN, SUMM, DRWD, DETD, CLM
FPBIB ----- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
RLI, PRAI, REP, REN, EXNAM, LREP, CLM, CLMN, DRWN
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its structure diagram
FPG ----- FP plus PAGE.DRAW
GI ----- PN and page image numbers
HIT ----- All fields containing hit terms
HITRN ----- HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
its structure diagram
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IALL ----- ALL, indented with text labels
IALLG ----- IALL plus PAGE.DRAW
IBIB ----- BIB, indented with text labels
IBIB.EX ----- IBIB for original and latest publication
IBIBG ----- IBIB plus PAGE.DRAW
IMAX ----- MAX, indented with text labels
IMAX.EX ----- IMAX for original and latest publication
IND ----- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU, OS, CC, SX, ST, IT
ISTD ----- STD, indented with text labels
KWIC ----- All hit terms plus 20 words on either side
MAX ----- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
EXF, ARTU OS, CC, SX, ST, IT

of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. **sulfonylureas**, and in more severe cases, insulin. However, the clinically available hypoglycemics can have other side effects which limit their use. . . .

- SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .
- SUMM This invention is directed to glycogen phosphorylase inhibitor compounds of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.
- SUMM Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound.
- SUMM . . . to a mammal suffering from hypercholesterolemia a hypercholesterolemia treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.
- SUMM Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;
- SUMM . . . or more antidiabetic agents such as insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; **Sulfonylureas** and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., glimepiride, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole,. . . 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; Phosphodiesterase Inhibitors: L-386,398; Lipid-lowering Agents: benfluorex; Antiobesity Agents: fenfluramine; Vanadate and **vanadium** complexes (e.g. naglivan.RTM.) and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents: nicotinic acid, acipimox, WAG. . .
- SUMM Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.
- SUMM . . . glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.
- SUMM . . . of 10 g tryptone, 5 g yeast extract, 5 g NaCl, and 1 ml 1N NaOH per liter) plus 100 mg/L ampicillin, 100 mg/L pyridoxine and 600 mg/L MnCl.sub.2 and grown at 37.degree. C. to a cell density of OD.sub.550 =1.0. At this point, the cells are induced. . .
- SUMM . . . immobilized on Affi-Gel 10 (BioRad Corp., Melville, N.Y.) as per the manufacturer's instructions. In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads (1 mL)

in 2.5 mL of 100 mM HEPES and 80 mM CaCl₂ at. . .

SUMM . . . PO₄ and 0.5 mM dithiothreitol. 20 μ L of this stock is added to 80 μ L of Buffer A containing 0.47 mg/mL glycogen, 9.4 mM glucose, 0.63 mM of the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP⁺). The compounds to be. . .

SUMM . . . MgCl₂ and 0.5 mM dithiothreitol. 20 μ L of this stock is added to 80 μ L of Buffer B with 1.25 mg/mL glycogen, 9.4 mM glucose, and 0.63 mM glucose-1-phosphate. The compounds to be tested are added as 5 μ L of solution. . . J., Reinach, P. S. and Candia, O. A. (1979) Anal. Biochem. 100, 95-97] modified as follows: 150 μ L of 10 mg/mL ammonium molybdate, 0.38 mg/mL malachite green in 1 N HCl is added to 100 μ L of the enzyme mix. After a 20 minute incubation. . .

SUMM . . . (a modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971)) (hexokinase method) using a 100 mg/dL standard. Plasma glucose is then calculated by the equation:

SUMM Plasma glucose (mg/dL)=Sample value \times 5 \times 1.784=8.92 \times imes.Sample value

SUMM The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., greater than or equal to 250 mg/dL), animals treated with test compounds at suitable doses have significantly depressed glucose levels. Hypoglycemic activity of the test compounds is. . .

SUMM . . . administered, the animals are sacrificed by decapitation and trunk blood is collected into 0.5 mL serum separator tubes containing 3.6 mg of a 1:1 weight/weight sodium fluoride: potassium oxalate mixture. The freshly collected samples are centrifuged for two minutes at 10,000 \times g. . .

SUMM . . . method; a modification of the method of Allain, et al. Clinical Chemistry 20, 470 (1974)) using a 100 and 300 mg/dL standards. Serum insulin, triglycerides, and total cholesterol levels are then calculated by the equations,

SUMM Serum triglycerides (mg/dL)=Sample value \times 2

SUMM Serum total cholesterol (mg/dL)=Sample value \times 2

SUMM The animals dosed with vehicle maintain substantially unchanged, elevated serum insulin (e.g. 225 μ U/mL), serum triglycerides (e.g. 225 mg/dL), and serum total cholesterol (e.g. 160 mg/dL) levels, while animals treated with test compounds of this invention generally display reduced serum insulin, triglycerides, and total cholesterol levels.. . .

SUMM . . . BB/W rats, or non-diabetic BB/W age matched control rats are pretreated with heparin (1000 u, i.p.), followed by pentobarbital (65 mg/kg, i.p.). After deep anesthesia is achieved as determined by the absence of a foot reflex, the heart is rapidly excised. . .

SUMM Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using. . .

SUMM . . . over, for example 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 mg/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then. . .

SUMM . . . lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the range of 0.005 to 50 mg/kg/day, preferably 0.01 to 25 mg/kg/day and most preferably 0.1 to 15 mg/kg/day.

DETD . . . polar material characterized by ¹H NMR as the corresponding N, O-bis (5-chloro-1H-indole-2-carbonyl derivative. The more polar desired substance (48 mg) was dissolved in a mixture of methanol and 0.25 mL 1N HCl, the resulting solution

concentrated, and the resulting solid triturated with ether giving the title substance (42 mg): HPLC (70/30) 80%, 2.53 minutes and 13%, 4.04 min, the latter corresponding in retention time to the N,O-bis O-acylated derivative.

DETD . . . at 25.degree. C. for 0.5 hours. The mixture was concentrated and the residue triturated with ether and dried: Yield 212 mg; HPLC (15/85) 2.85 min; PBMS 278 (MH+, 100%).

DETD N-Methylpiperazine (75 mg, 0.75 mmol) and (2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-4-phenyl-butyric acid (0.200 g, 0.68 mmol) were coupled according to Procedure A giving a colorless foam which was used without purification: Yield 225 mg, 88%; PBMS 378 (MH+, 100%);

DETD . . . A (except at 0-25.degree. C.). The crude product was dissolved in dichloromethane and the resulting solution stirred with approx 200 mg dimethylaminopyridine-polystyrene resin (Aldrich Chemical Co., Milwaukee, Wis.) for 1 hour, filtered, and concentrated giving the product as a colorless solid: . . .

DETD ((1S)-[(R)-Hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl)-carbamic acid tert-butyl ester (791 mg, 2.3 mmol) was dissolved in 4M HCl-dioxanes for 45 minutes at 25.degree. C. for 45 min, the mixture concentrated, the residue coevaporated with ether, suspended in ether and filtered giving 583 mg (91%) of the title substance.

DETD . . . with 6N HCl and extracted with ethyl acetate. The extracts were dried and concentrated giving a light brown solid (458 mg, 34%): HPLC (60/40) 5.31 (93%).

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 mg 70%; HPLC (60/40) 3.09 minutes (97%).

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-4-phenyl-butyric acid (357 mg, 1.0 mmol) and N,O-dimethylhydroxylamine hydrochloride, 98% (98 mg, 1.0 mmol) were coupled according to procedure A (dimethylformamide solvent). The foam obtained was triturated with ether, the sticky solid dissolved in dichloromethane, concentrated and triturated with hexanes: yield 215 mg, 54%; HPLC (60/40) 6.38 minutes (98%); PBMS 400/402 (MH+, 100%);

DETD . . . the mixture was filtered and the filtrate carried on in the usual manner of Procedure A). The crude product (920 mg) was dissolved in methanol and treated with 1N NaOH (6.6 mL) for 2 hours at 25.degree. C. 1N NaOH was . . . brine, dried, and concentrated. The resulting colorless solid was stirred in chloroform and filtered giving the title substance: Yield 763 mg, 40%; HPLC (60/40) 2.86 minutes (89%); mp 214-215.degree. C.; PBMS 283/285 (MH+, 100%); .sup.1 H NMR (DMSO-d.sub.6) .delta.11.78 (s, 1H), . . .

DETD (1S,2R)-(1-Benzyl-2-dimethylcarbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (283 mg, 0.84 mmol) was dissolved in 4N HCl-dioxane (1 mL) for 1.5 hours at 25.degree. C., concentrated and the residue coevaporated. . .

DETD Sodium hydride-oil dispersion (53 mg of 50%) was added to a solution of (1S,2R)-(1-benzyl-2-dimethylcarbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (322 mg, 1.0 mmol) in tetrahydrofuran (4 mL) at 0.degree. C. After effervescence ceased (several minutes), methyl iodide (155 mg) was added, and after 15 minutes another 11 mg NaH dispersion and 23 mg methyl iodide were added. After 15 more minutes aqueous ammonium chloride solution and ethyl acetate were added, and the organic. . . washed with water, 2N NaOH, dried and concentrated giving a viscous oil which was used without further purification: Yield 283 mg, 84%.

DETD (3S)-tert-Butoxycarbonylamino-(2R)-hydroxy-4-phenyl-butyric acid (Schweizerhall, Inc., S. Plainfield, N.J., 1.02 g, 3.4 mmol) and dimethylamine hydrochloride (338 mg, 4.1 mmol) were coupled

according to Procedure A (0-25.degree. C., dimethylformamide-dichloromethane solvent, acid, then base extraction) giving crude product which was chromatographed on silica eluted with 1-8% ethanol in dichloromethane: Foam; Yield 995 mg, 91%;

DETD (1S,2R)-(1-Benzyl-2-methoxy-methyl-carbamoyl-2-methoxy-ethyl)-carbamic acid tert-butyl ester (113 mg, 0.32 mmol) was dissolved in 4N HCl-dioxane (4 mL) at 25.degree. C. for 1 hour, concentrated, and the residue triturated with ether giving the title product (93 mg, 100%).

DETD Sodium hydride dispersion (30 mg of 50% in oil) was added to a solution of (1S,2R)-(1-Benzyl-2-methoxy-methyl-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester in tetrahydrofuran (2 mL) at 0.degree. C. After 5 minutes methyl iodide (175 mg) was added and the mixture was allowed to stand at 25.degree. C. for 18 hour. Ethyl acetate and saturated aqueous. . . organic layer was separated, washed with water, dried, concentrated, and chromatographed on silica eluting with 10-20% ethyl acetate-hexanes: Yield 113 mg, 52%; HPLC (60/40) 6.45 minutes (>96%).

DETD (1R,2S)-[2-Amino-1-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester hydrochloride (162 mg, 0.38 mmol) was coupled with 5-chloro-1H-indole-2-carboxylic acid (71 mg, 0.36 mmol) according to Procedure A (0-25.degree. C. reaction temperature) and the crude product purified by chromatography on silica gel. . .

DETD (1R,2S)-[2-tert-Butoxycarbonylamino-1-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester (170 mg, 0.35 mmol) was dissolved in 4N HCl-dioxane (2 mL) for 1.5 hours at 25.degree. C., concentrated, the residue coevaporated with ether and dried giving an oil (163 mg). MS 387 (MH+, 100%).

DETD Sodium hydride dispersion (120 mg of 50% in oil, 2.8 mmol) was added to a solution of (1S,2R)-(1-benzyl-2-methoxy-methyl-carbamoyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (858 mg, 2.5 mmol) in tetrahydrofuran (8 mL) at 0.degree. C. After effervescence ceased benzyl bromoacetate (0.56 g, 2.5 mmol) was added and the mixture was brought to 25.degree. C. After 2 hours more NaH dispersion was added (12 mg), and the mixture was stirred 1 hour, diluted with ethyl acetate and saturated ammonium chloride, the organic layer separated, washed. . . was chromatographed on silica gel eluted with 20-75% ethyl acetate-hexanes. The most pure fractions were combined giving an oil (175 mg, 15%): MS 487 (MH+), 387 (100%).

DETD A mixture of [(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(1R)-(methoxy-methyl-carbamoyl)-3-phenyl-propoxy]-acetic acid benzyl ester (120 mg, 0.2 mmol) and 50% moist palladium hydroxide on carbon catalyst in methanol (50 mL) was shaken at 40 p.s.i. hydrogen. . . mixture was allowed to stand for 30 min, then filtered through a filter aid and the filtrate concentrated giving 121 mg of a solid which was chromatographed on silica and eluted with 25-100% ethyl acetate-hexanes giving 84 mg of a solid, HPLC (60/40) 4.81 (37%) and 6.24 minutes (63%). .sup.1 H NMR and MS analysis showed these to. . . separated, washed with water, dried, and concentrated giving a mixture of the title substance and the des-5-Cl analog: Yield 85 mg, 71%; HPLC (60/40) 3.49 minutes (37%), 4.23 minutes (61%); MS 338 (MH+, 100%); TSPMS 474/476 (MH+for title substance, 40%), 440. . .

DETD . . . fluoride (0.30 g, 1.29 mmol) was added to a solution of (2S,3S)-3-amino-2-hydroxy-4-phenyl-butyramide hydrochloride (0.319 g, 1.61 mmol) and triethylamine (145 mg, 1.42 mmol) in dichloromethane (2 mL) at 25.degree. C. After 18 hours the mixture was diluted with ethyl acetate, the. . .

DETD . . . for 1 hour. The mixture was concentrated and the residue triturated with ether and dried giving a colorless solid (430 mg): HPLC (60/40) 2.68 min, 100%.

DETD Aqueous 1N NaOH (2.6 mL) was added to a solution of (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2S)-hydroxy-4-phenylbutyric acid methyl ester

(500 mg, 1.29 mmol) in methanol at 25.degree. C. After 18 hours the mixture was concentrated, the residue dissolved in ethyl acetate. . . layer was separated, extracted three times with ethyl acetate, the organic layers combined, dried and concentrated giving a solid (417 mg, 87%): HPLC (60/40) 4.23 (>98%).

DETD [1(S)-Benzyl-(2S)-((tert-butyl-dimethyl-silyloxy)-2-cyano-ethyl)-carbamic acid tert-butyl ester (417 mg) was added to a solution of anhydrous HCl (3.2g) in methanol (20 mL) and the resulting solution capped and kept at 25.degree. C. for 5 days. The mixture was concentrated to give 308 mg of colorless solid which was homogeneous by ¹H NMR (D₂O). This material was combined with spectrally equivalent material prepared in the same manner from 400 mg of the same precursor, and together the mixture was dissolved in saturated aqueous NaHCO₃ which was extracted ten times with chloroform. The combined extracts were dried and concentrated giving the title substance (328 mg, 75%):

DETD A solution of (3S)-[(5-fluoro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (190 mg, 0.5 mmol), 1N NaOH (1 mL) and methanol (5 mL) was stirred at 25.degree. C. for 18 hours. The pH. . . water at 25.degree. C. and filtered. The resulting solid was washed with ether and dried giving a colorless glass (160 mg, 87%): HPLC (60/40) 3.49 minutes (99%); ¹H NMR (partial, DMSO-d₆) δ 8.15 (d, 1H, J=8 Hz), 7.42 (m, 2H), 7.3. . .

DETD Aqueous 1N NaOH (1.18 mL) was added to a suspension of (3S)-[(5,6-dichloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (249 mg, 0.6 mmol) in methanol (5 mL) at 25.degree. C. After 18 hours the mixture was concentrated, the residue partitioned between. . . washed with ethyl acetate, the combined organic layers washed with brine, dried and concentrated giving a yellow solid: Yield 259 mg; HPLC (60/40) 4.96 minutes (100%); TSPMS 407/409 (MH⁺, 100/40%);

DETD Aqueous 1N NaOH (1.69 mL) was added to a suspension of (3R)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenyl-butyric acid methyl ester (326 mg, 0.8 mmol) in methanol at 25.degree. C. After 2.5 hours the mixture was concentrated (starting material found) and redissolved in. . . and the residue partitioned between excess 2N HCl and ethyl acetate, the organic layer separated, dried and concentrated: Yield 288 mg, 92%; HPLC (60/40) 3.89 minutes (93%); mp 215-223.degree. C.; TSPMS 373/375 (MH⁺, 100%);

DETD (2R,3R)-3-Amino-2-hydroxy-4-phenylbutyric acid methyl ester hydrochloride (239 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (200 mg, 1.05 mmol) were coupled according to Procedure A (0-25.degree. C., washed with acid, then base) giving crude product which was used without further purification: Yield 328 mg, 87%.

DETD A mixture of (2R,3R)-3-amino-2-hydroxy-4-phenylbutyric acid (200 mg, 1.0 mmol, Sigma Chemical Co. (St. Louis, Mo.), chlorotrimethylsilane (500 mg, 4.6 mmol) and methanol (2 mL) was heated at reflux for 5.5 hours and concentrated to a foam: Yield 244 mg, 100%.

DETD A large excess of anhydrous ammonia was introduced into a solution of (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid methyl ester (100 mg, 0.27 mmol) in methanol (10 mL) and the mixture was heated in a stainless steel Parr reactor (<50 p.s.i.) for. . .

DETD Dimethylamine hydrochloride (262 mg, 3.22 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid (1.0 g, 2.68 mmol) were coupled in DMF (4 mL) using triethylamine (530 mg, 3.22 mmol), 1-hydroxybenzotriazole hydrate (612 mg, 4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at 25.degree. C. for 18 hours. The mixture was diluted with chloroform (80 mL) and. . . 10 mL cold ether

and filtered, washing with 5 mL cold ether giving after drying a colorless solid: Yield 715 **mg**, 67%); mp 190-192.degree. C.; HPLC (60/40) 4.53 minutes (100%); FABMS 400/402 (MH+, 80%), 178 (100%);

DETD N-Methylhydroxylamine hydrochloride (167 **mg**, 2.0 mmol) and (3S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid (373 **mg**, 1.0 mmol) were coupled according to Procedure A (DMF solvent, base wash omitted) and the crude product purified by chromatography. . .

DETD . . . Procedure A. The mixture was purified by chromatography on silica eluting with 33-50% ethyl acetate-hexanes giving the title substance (100 **mg**) and the more polar major substance 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide (970 **mg**), plus a mixture of the two substances (159 **mg**, mostly more polar product). For the title substance: PBMS 593/595 (MH+, 60%), 400(100%);

DETD . . . hydrochloride (0.39 mmol) and (3S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid (0.32 mmol) were coupled according to Procedure A (0-25.degree. C.) The crude product (159 **mg**) was stirred with 200 **mg** polystyrene-DMAP resin (Aldrich Chemical Co., Milwaukee, Wis.) in dichloromethane for 1 hour at 25.degree. C., filtered and the filtrate concentrated: . . .

DETD 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC, 790 **mg**, 4.12 mmol), dichloroacetic acid (136 **mg**, 1.06 mmol) and 5-chloro-1H-indole-2-carboxylic acid {(1S)-[(R)-hydroxy-(methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-amide (287 **mg**, 0.69 mmol) were added, in this order, to a solution of anhydrous dimethylsulfoxide (4 mL) and toluene (anhydrous, 4 mL). . . HCl, and saturated aqueous NaHCO.sub.3. The organic layer was dried, concentrated and the resulting foam recrystallized from ether. Yield, 100 **mg**, 35%; HPLC (60/40) 10.72 minutes (87%), starting material eluted at 6.68 minutes in this run and was present at less. . .

DETD {1(R)-[Hydroxy-((S)-methoxy-methyl-carbamoyl)-methyl]-2-phenyl-ethyl}-carbamic acid (285 **mg**, 0.8 mmol) was dissolved in cold 4N HCl-dioxane and the resulting solution stirred for 1 hour at 0.degree. C. The mixture was concentrated and the residue triturated with ether and dried giving 207 **mg** (90%) of a solid.

DETD (2S,3R)-3-(t-Butoxycarbonylamino)-2-hydroxy-4-phenylbutyric acid (300 **mg**, 1.0 mmol, Sigma Chemical Co., St. Louis, Mo.)) and N,O-dimethylhydroxylamine hydrochloride (104 **mg**, 1.1 mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature): Yield 88%; HPLC (60/40) 4.90 minutes (95%);

DETD m-Chloroperoxybenzoic acid (62 **mg** of 50%, 0.18 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid {(1S)-benzyl-(2R)-hydroxy-3-oxo-3-thiazolidin-3-yl-propyl)-amide (80 **mg**, 0.18 mmol) in dichloromethane (2 mL). After 1 hour the mixture was poured into a mixture of saturated aqueous sodium . . . acetate. The organic layers were combined, washed with saturated aqueous sodium bicarbonate, dried, and concentrated giving a yellow solid (80 **mg**, 96%): HPLC (60/40) 3.37 (97%); PBMS 460/462 (MH+, 100%).

DETD m-Chloroperoxybenzoic acid (45 **mg** of 50%, 0.13 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid {(1S)-benzyl-(2R)-hydroxy-3-oxo-3-thiomorpholin-4-yl-propyl)-amide (60 **mg**, 0.13 mmol) in dichloromethane (1.5 mL). After 1 hour the mixture was poured into a mixture of saturated aqueous sodium . . . title sulfoxide (Example 70) as a yellow solid which was chromatographed on silica gel eluting with 1% ethanol-dichloromethane: Yield 44 **mg**, 72%; HPLC (60/40) 6.14 minutes (98%). PBMS 474/476 (MH+, 100%). A less polar product (8 **mg**) identified as the title sulfone (Example 71) was also isolated: HPLC (60/40) 6.44 minutes (96%). PBMS 490/492 (MH+, 100%).

DETD Lithium hydroxide solution (0.2 mL of 1N in water) was added to a solution of 1-((3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-

4-phenyl-butyryl)-piperidine-4-carboxylic acid ethyl ester (111 mg, 0.22 mmol) in tetrahydrofuran (2 mL) at 25.degree. C. After 18 hours the mixture was concentrated and the residue triturated. . . 6N HCl was added to attain a pH of 1. The organic layer was separated, dried and concentrated giving 109 mg (100%) of a solid: HPLC (60/40) 3.79 minutes (99%);

DETD Trifluoroacetic acid (2 mL) was added to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-tert-butoxycarbonyl-hydroxy-methyl)-2-phenyl-ethyl]-amide (256 mg, 0.58 mmol) in dichloromethane (2 mL) and the resulting solution was stirred for 18 hours at 25.degree. C. More trifluoroacetic. . . with 2.5%, 5%, 10% ethanol-dichloromethane containing 1% acetic acid. The purified product was triturated with ether-hexanes and dried: Yield 70 mg, 31%; HPLC (60/40) 3.11 (96%);

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)amino]-(2R)-hydroxy-4-phenylbutyric acid (310 mg, 0.8 mmol) and (1-benzyl-piperidin-4-yl)-methylamine hydrochloride (EPO publication 0 457 686, example 1A therein, 200 mg, 0.8 mmol) were coupled according to Procedure A (dimethylformamide solvent). The crude product was purified by chromatography on silica gel eluted with 0.5-4% ethanol in dichloromethane containing 0.5% ammonium hydroxide giving a colorless foam: yield 140 mg, 30%; HPLC (60/40) 4.15 minutes (95%); TSPMS 559/562 (MH+, 100%);

DETD (3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyric acid (1.0 g, 2.6 mmol) and 4-methylamino-piperidine-1-carboxylic acid tert-butyl ester (575 mg, 2.6 mmol) were coupled according to Procedure A (dimethylformamide solvent). The crude product was purified by chromatography on silica gel eluted with 20, 30, 40, 50, and 75% ethyl acetate-hexanes: yield 319 mg, 21%; HPLC (60/40) 10.31 minutes (94%); 569/571 (MH+, 100%).

DETD 4-((3S)-[(5-Chloro-1H-indole-2-carbonyl)-amino]-(2R)-hydroxy-4-phenylbutyryl)-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester (292 mg, 0.5 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. and stirred for 1 hour at room temperature. The mixture was concentrated and the residue triturated with ether and dried: yield 249 mg, 96%; HPLC (60/40) 2.59 minutes (96%). PBMS 469/471 (MH+, 100%);

DETD Molecular sieves (3 .ANG. powdered, 100 mg), triethylamine (22 mg, 0.2 mmol), glacial acetic acid (64 mg, 1.1 mmol), sodium cyanoborohydride (95%, 18 mg, 0.3 mmol), and aqueous formaldehyde (37 weight % in water, 22 mg, 0.3 mmol) were added sequentially to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-[(R)-hydroxy-(methyl-piperidin-4-yl-carbamoyl)-methyl]-2-phenyl-ethyl]-amide hydrochloride (100 mg, 0.2 mmol) in methanol (2 mL) at 25.degree. C. After 18 hours the reaction mixture was filtered thru Celite.RTM., the. . . solid residue was purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane giving a colorless solid (93 mg, 91%). This material was dissolved in methanol at 0.degree. C., the resulting solution treated with 1.01 N HCl (0.21 mL), and the resulting solution immediately concentrated. The residue was triturated with ether and dried: yield 87 mg, 79%; HPLC (60/40) 2.86 minutes (95%); TSPMS 483/485 (MH+, 100%);

CLM What is claimed is:

21. The method as recited in claim 19 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 1.

. . . a glycogen phosphorylase inhibitor as recited in claim 30; b) an antidiabetic agent selected from insulin and insulin analogs; insulinotropin; **Sulfonylureas** and analogs; Biguanides; .alpha.2-Antagonists and Imidazolines; insulin secretagogues;

Glitazones; Fatty Acid Oxidation inhibitors; .alpha.-Glucosidase inhibitors; .beta.-Agonists; Phosphodiesterase Inhibitors; Lipid-lowering Agents; Antiobesity Agents; Vanadate and **vanadium** complexes and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents; and c) optionally a pharmaceutically acceptable.

37. A method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a therapeutically effective amount of a compound of claim 30.

45. A method for treating Type I **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

47. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

49. A method for treating Type II **diabetes** in a mammal which comprises administering to a mammal a therapeutically effective amount of a compound of claim 30.

L8 ANSWER 2 OF 3 USPATFULL

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AB . . . R.sub.9 or C(O)R.sub.12 as glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

SUMM This invention relates to glycogen phosphorylase inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to treat **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

SUMM In spite of the early discovery of insulin and its subsequent widespread use in the treatment of **diabetes**, and the later discovery of and use of **sulfonylureas** (e.g. Chlorpropamide.TM. (Pfizer), Tolbutamide.TM. (Upjohn), Acetohexamide.TM. (E. I. Lilly), Tolazamide.TM. (Upjohn)) and biguanides (e.g. Phenformin.TM. (Ciba Geigy), Metformin.TM. (G. D. Searle)) as oral hypoglycemic agents, the treatment of **diabetes** remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective Type I **diabetes**, insulin dependent **diabetes** mellitus), requires multiple daily doses, usually by self injection. Determination of the proper dosage of insulin requires frequent estimations of. . . causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Treatment of non-insulin dependent **diabetes** mellitus (Type II **diabetes**, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. **sulfonylureas**, and in more severe cases, insulin. However, the clinically available hypoglycemics can have other side effects which limit their use.. . .

SUMM . . . whom the causative agent or disorder is unknown. While such "essential" hypertension is often associated with disorders such as obesity, **diabetes** and hypertriglyceridemia, the relationship between these disorders has not been elucidated. Additionally, many patients display the symptoms of high blood. . .

SUMM This invention is directed to a glycogen phosphorylase inhibitor

compound of Formula I useful for the treatment of **diabetes**, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hypertension, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM Yet another aspect of this invention is directed to a method for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a Formula I compound. Included in the treatment of **diabetes** is the prevention or attenuation of long term complications such as neuropathy, nephropathy, retinopathy or cataracts.

SUMM Another aspect of this invention is directed to pharmaceutical compositions for the treatment of **diabetes** which comprise a therapeutically effective amount of a glycogen phosphorylase inhibitor;

SUMM . . . or more antidiabetic agents such as insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ; **Sulfonylureas** and Analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide.RTM., glimepiride, repaglinide, meglitinide; Biguanides: metformin, phenformin, buformin; .alpha.2-Antagonists and Imidazolines: midaglizole, isaglidole, . . . 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; Phosphodiesterase Inhibitors: L-386,398; Lipid-lowering Agents: benfluorex; Antiobesity Agents: fenfluramine; Vanadate and **vanadium** complexes (e.g. naglivan.RTM.) and peroxovanadium complexes; Amylin Antagonists; Glucagon Antagonists; Gluconeogenesis Inhibitors; Somatostatin Analogs; Antilipolytic Agents: nicotinic acid, acipimox, WAG. . .

SUMM Another aspect of this invention is a method of treating **diabetes** in a mammal with the above described combination compositions.

SUMM . . . glycogen molecule. These disorders are ameliorated by reduction of or characterized by an elevation of glycogen phosphorylase activity. Examples include **diabetes**, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and myocardial ischemia.

SUMM . . . of 10 g rypstone, 5 g yeast extract, 5 g NaCl, and 1 ml 1N NaOH per liter) plus 100 mg/L ampicillin, 100 mg/L pyridoxine and 600 mg/L MnCl.sub.2 and grown at 37.degree. C. to a cell density of OD.sub.550 =1.0. At this point, the cells are induced. . .

SUMM . . . immobilized on Affi-Gel 10 (BioRad Corp., Melville, N.Y.) as per the manufacturer's instructions. In brief, the phosphorylase kinase enzyme (10 mg) is incubated with washed Affi-Gel beads (1 mL) in 2.5 mL of 100 mM HEPES and 80 mM CaCl.sub.2 at. . .

SUMM . . . PO.sub.4 and 0.5 mM dithiothreitol. 20 .mu.l of this stock is added to 80 .mu.l of Buffer A containing 0.47 mg/mL glycogen, 9.4 mM glucose, 0.63 mM of the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP.sup.+). The compounds to be. . . MgCl.sub.2 and 0.5 mM dithiothreitol. 20 .mu.l of this stock is added to 80 .mu.l of Buffer B with 1.25 mg/mL glycogen, 9.4 mM glucose, and 0.63 mM glucose-1-phosphate. The compounds to be tested are added as 5 .mu.l of solution. . . L. J., Reinach, P. S. and Candia, O. A. (1979) Anal. Biochem. 100, 95-97] modified as follows: 150 .mu.of 10 mg/mL ammonium molybdate, 0.38 mg/mL malachite green in 1N HCl is added to 100 .mu.l of the enzyme mix. After a 20 minute incubation at. . .

SUMM . . . (a modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971)) (hexokinase method) using a 100 mg/dL standard. Plasma glucose is then calculated by the equation:

SUMM Plasma glucose (mg/dL)=Sample value.times.5.times.1.784=8.92.times.Sample value

SUMM The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., greater than or equal to 250

mg/dL), animals treated with test compounds at suitable doses have significantly depressed glucose levels. Hypoglycemic activity of the test compounds is. . .

SUMM . . . administered, the animals are sacrificed by decapitation and trunk blood is collected into 0.5 mL serum separator tubes containing 3.6 mg of a 1:1 weight/weight sodium fluoride: potassium oxalate mixture. The freshly collected samples are centrifuged for two minutes at 10,000.times.. . .

SUMM . . . method; a modification of the method of Allain, et al. Clinical Chemistry 20, 470 (1974)) using a 100 and 300 mg/dL standards. Serum insulin, triglycerides, and total cholesterol levels are then calculated by the equations,

SUMM Serum triglycerides (mg/dL)=Sample value.times.2

SUMM Serum total cholesterol (mg/dL)=Sample value.times.2

SUMM The animals dosed with vehicle maintain substantially unchanged, elevated serum insulin (e.g. 225 .mu.U/mL), serum triglycerides (e.g. 225 mg/dl), and serum total cholesterol (e.g. 160 mg /dL) levels, while animals treated with test compounds of this invention generally display reduced serum insulin, triglycerides, and total cholesterol levels.. . .

SUMM . . . BB/W rats, or non-diabetic BB/W age matched control rats are pretreated with heparin (1000 u, i.p.), followed by pentobarbital (65 mg/kg, i.p.). After deep anesthesia is achieved as determined by the absence of a foot reflex, the heart is rapidly excised. . .

SUMM Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using. . .

SUMM . . . over, for example 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 mg/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then. . .

SUMM . . . lowering activities and hyperinsulinemia reversing activities of the compounds of this invention is in the range of 0.005 to 50 mg/kg/day, preferably 0.01 to 25 mg/kg/day and most preferably 0.1 to 15 mg/kg/day.

DETD . . . with 2N HCl, 2N NaOH, 2N HCl, dried, triturated with 1:1 ether/hexanes and dried, giving an off-white solid: Yield 280 mg, 73%; HPLC (60/40) 4.66 minutes (96%); PBMS 322/324 (MH+, 100%).

DETD . . . sequence was repeated and the resulting solids were suspended in EtOAc, stirred for 1 hour, filtered and dried: Yield 252 mg, 88%; HPLC (60/40) 2.33 minutes (93%); TSPMS 338/340 (MH+, 100%);

DETD . . . filtered and the collected solid washed successively with aqueous 2N HCl, aqueous 2N NaOH, ether and dried : Yield 180 mg, 68%; TSPMS 336/338 (MH+, 100%);

DETD . . . purified by column chromatography on silica gel eluted with 0.5-16% ethanol in dichloromethane to give a colorless foam: Yield 260 mg, 63%; HPLC (60/40) 100%, 3.86 minutes; PBMS 412/414 (MH+, 100%);

DETD . . . residue purified by column chromatography on silica gel eluted with 10, 20 and 30% ethyl acetate in hexanes: Yield 14 mg, 6%; HPLC (60/40) 8.88 minutes (98%); PBMS 398/400 (MH+, 100%);

DETD . . . by column chromatography on silica gel eluted with 30% ethyl acetate in hexanes to give a colorless foam: Yield 290 mg, 95%; HPLC (70/30) 6.23 min (99%); PBMS 512/514 (MH+, 100%);

DETD . . . desired fractions concentrated, the residue dissolved in chloroform and methanol and the resulting solution stirred 18 hours with approx. 128 mg dimethylaminopyridine-polystyrene resin (Fluka Chemical Co.). The solution was filtered, concentrated and the residue triturated with ether: Yield, 51%; HPLC (60/40). . .

DETD . . . reaction temperature). The crude product was dissolved in

chloroform and methanol and the resulting solution stirred 18 hours with 50 mg dimethylaminopyridine-polystyrene resin (Fluka Chemical Co.), the solution filtered, concentrated and the solids triturated with ether: Yield 83%; HPLC (60/40) 8.88. . .

DETD . . . acetate, the resulting solution washed with 2N NaOH and 2N HCl, the suspension filtered and the solids dried: Yield 111 mg, 26%; HPLC (60/40) 8.88 minutes (92%); PBMS 424/426 (MH+, 100%); mp 258-261.degree. C.; PBMS 424/426 (MH+, 100%);

DETD . . . to procedure A (0-25.degree. C. reaction temperature, 140 hour reaction time) and the crude product triturated with ether: Yield 89 mg, 71%; HPLC (70/30) 7.57 minutes (98%); PBMS 396/398 (MH+, 100/80%);

DETD . . . the product purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane containing 0.5% ammonium hydroxide: Yield 86 mg, 69%; HPLC (40/60) 7.57 minutes (>99%); mp 187-190.5.degree. C.; TSPMS 441/443 (MH+, 100%);

DETD . . . Na.sub.2 SO.sub.4, and concentrated. The residue was stirred under ether for 1 hour, the solid filtered and dried: Yield 125 mg, 87%; HPLC (60/40) 2.85 minutes (98%); PBMS 469/471 (MH+, 100/90%);

DETD . . . temperature, 60 hour reaction time, washed first with acid, then base), and the resulting solid triturated with ether: Yield 320 mg, 99%; HPLC (60/40) 5.87 minutes (100%);

DETD . . . ethyl acetate and 2N NaOH, the resulting suspension filtered, the solids washed with ethyl acetate, water and dried: Yield 135 mg, 40%; HPLC (40/60) 7.29 minutes (98%); TSPMS 338/340 (MH+, 100%);

DETD . . . according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes: Yield 241 mg, 50%; HPLC (60/40) 7.67 minutes (94%);

DETD . . . with 0.20 mL 4N HCl in dioxane. A precipitate formed which was filtered, washed with dichloromethane and dried: Yield 220 mg, 42%; HPLC (60/40) 3.19 minutes (96%);

DETD . . . according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes: Yield 302 mg, 59%; PBMS 511/513 (MH+, 100%);

DETD . . . to Procedure A. The resulting solid was suspended in ether, filtered and dried to give a beige solid: Yield, 264 mg, 71%; HPLC (60/40) 3.28 minutes (100%); TSPMS 322/324 (MH+, 100%);

DETD . . . (1.0 mmol) were coupled according to Procedure A. The resulting solid was suspended in ether, filtered and dried: Yield 158 mg, 53%; PBMS 296/298 (MH+, 100%);

DETD . . . on silica gel eluted with 5-30% ethanol in dichloromethane containing 0.5% ammonium hydroxide, followed by trituration with ether: Yield 21 mg, 5%; PBMS 453/455 (MH+, 100%);

DETD . . . layer separated and washed with brine, dried over Na.sub.2 SO.sub.4, concentrated and the resulting solid triturated with ether: Yield 189 mg, 77%; HPLC (60/40) 2.63 minutes (99%);

DETD . . . The resulting solution was stirred at 25.degree. C. for 0.5 hours, concentrated and the residue triturated with ether: Yield 190 mg, 85%; HPLC (60/40) 2.62 minutes (98%); PBMS 411/413 (MH+, 100%);

DETD . . . reaction was concentrated and the residue triturated first with ether then with a mixture of ether and hexanes. Yield 360 mg, 82%; HPLC (60/40) 4.84 minutes (99%); PBMS 440/442 (MH+, 40%), 396/398 (MH-44, 100%);

DETD . . . to Procedure A and the crude product purified by chromatography on silica gel eluting with 1:2 ethyl acetate-hexanes: Yield 611 mg, 62%; HPLC (60/40) 13.45 minutes (57%) and 14.46 minutes (41%).

DETD . . . reaction solvent dimethylformamide). The crude product was stirred in ether for 0.5 hours then filtered giving a beige solid: 182

mg, 98%; HPLC (60/40) 3.41 minutes (98%); mp >260.degree. C. (dec); TSPMS 363/365 (MH+, 100%);

DETD (S)-(1-Methylcarbamoyl-2-thiazol4-yl-ethyl)-carbamic acid tert-butyl ester (248 mg, 0.87 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. The resulting mixture was stirred for 1 hour at 25.degree..

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature, acid wash omitted) and the product used without further purification. Yield, 250 mg, 88%.

DETD . . . product purified by chromatography on silica gel eluted with 10, 20, 40 and 60% ethyl acetate in hexanes: Yield 565 mg, 95%; HPLC (60/40) 3.46 minutes (98%); mp 153-155.degree. C.; TSPMS 297/299 (MH+, 100/40%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature) and the crude product triturated first with 1:1 ether-hexanes, then with hexanes. Yield 115 mg, 75%; HPLC (60/40) 3.72 minutes (99%); mp 198-202.degree. C. (shrinks on insertion at 192.degree. C.); PBMS 377/379 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 124 mg, 41%.

DETD . . . to Procedure A and the product purified by chromatography on silica gel eluted with 2-10% ethanol in dichloromethane. Yield 180 mg, 86%; HPLC (60/40) 3.14 minutes (98%); TSPMS 428/430 (MH+, 100%);

DETD . . . purified by chromatography on silica gel eluted with 25, 40, 50, 75 and 100% ethyl acetate in hexanes. Yield 330 mg, 94 %; HPLC (60/40) 4.18 minutes (97%); TSPMS 450/452 (MH+, 100%).

DETD . . . residue was purified by chromatography on silica gel eluted with 1-50% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 217 mg, 80%.

DETD . . . with acid only) and the product purified by chromatography on silica gel eluted with 1-4% ethanol in dichloromethane. Yield 516 mg, 52%; HPLC (60/40) 5.33 minutes (93%).

DETD . . . acetate and 2N NaOH, the resulting precipitate was collected and washed with 2N NaOH, 1N HCl and water. Yield 135 mg, 42%; HPLC (60/40) 2.97 minutes (97%); PBMS 322 (MH+, 100%);

DETD . . . by chromatography on silica gel eluted with 20, 30, 40, 50, 75 and 100% ethyl acetate in hexanes. Yield 228 mg, 84%; HPLC (60/40) 3.57 minutes (98%); PBMS 410 (MH+, 100%);

DETD . . . purified by chromatography on silica gel eluted with 20, 30, 40, 50 and 75% ethyl acetate in hexanes. Yield 189 mg, 95%; HPLC (60/40) 4.76 minutes (97%); PBMS 414 (MH+, 100%);

DETD . . . suspension stirred at 25.degree. C. for 1 hour. The mixture was concentrated and the residue triturated with ether. Yield, 776 mg, 88%; HPLC (60/40) 2.31 minutes (99%).

DETD . . . product purified by chromatography on silica gel eluted with 20, 30, 40 and 50% ethyl acetate in hexanes. Yield 404 mg, 94%; HPLC (60/40) 4.74 min (98%); PBMS 430 (MH+, 100%);

DETD . . . C. The solution was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 866 mg, 84%.

DETD . . . by chromatography on silica gel eluted with 20, 30 and 40% ethyl acetate in hexanes giving a colorless foam (979 mg, 89% yield).

DETD . . . washed with 2N HCl, 2N NaOH and water. The filtered solid was boiled in acetone, filtered and dried. Yield 134 mg, 40%; HPLC (60/40) 3.06 minutes (97%); mp 239-241.degree. C. (with discoloration); PBMS 340 (MH+, 70%), 357 (100%)

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 mg (70%); HPLC (60/40) 3.09 minutes (97%).

DETD . . . mmol) were coupled according to Procedure A (0-25.degree. C. reaction temperature) and the product triturated with 1:1 ether-hexanes. Yield 213 **mg**, 92%; HPLC (60/40) 4.15 minutes (99%); PBMS 412 (MH+, 100%);

DETD . . . the resulting precipitate was collected by filtration followed by washing with 2N HCl, 2N NaOH, water and ether. Yield 110 **mg**, 52%; HPLC (60/40) 3.37 minutes (99%); mp 236-239.degree. C. (dec); PBMS 356/358 (MH+, 100%);

DETD . . . ethyl acetate and 2N HCl, filtered, and the filtered solid washed with 2N HCl, 2N NaOH and ether. Yield 988 **mg**, 98%; HPLC (70/30) 3.25 minutes (99%); mp 253-255.degree. C. (dec, darkening at 243.degree. C.); PBMS 324/326 (MH+, 100%);

DETD . . . gel eluted with 50, 75 and 100 % ethyl acetate in hexanes followed by trituration from 1:1 ether-hexanes. Yield 266 **mg**, 76%; HPLC (60/40) 4.09 minutes (99%); PBMS 426/428 (MH+, 100%);

DETD . . . ethyl acetate in hexanes. The product was collected as an off-white foam and triturated with 1:1 ether-hexanes to give 107 **mg**, 73%; HPLC (60/40) 6.21 minutes (99%); PBMS 490/492 (MH+, 100%);

DETD . . . eluted with 40 and 50% ethyl acetate in hexanes, followed by trituration of the resulting foam with ether. Yield 112 **mg**, 45%; HPLC (60/40) 5.13 minutes (>99%); PBMS 410/412 (MH+, 100%);

DETD (S)-[1-Benzyl-2-oxo-2-(3-oxo-pyrrolidin-1-yl)-ethyl]-carbamic acid tert-butyl ester (552 **mg**, 1.7 mmol) was dissolved in 4M HCl-dioxane (6.2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether to give a light brown solid. Yield, 482 **mg**, 108%.

DETD . . . reaction time, washed with acid first then base). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 966 **mg**, 91%; HPLC (60/40) 7.99 minutes (97%); PBMS 414/416 (MH+, 100%);

DETD . . . silica gel eluted with 30, 40 and 50% ethyl acetate in hexanes followed by trituration with 1:1 ether-hexanes. Yield 266 **mg**, 75%; HPLC (60/40) 5.52 minutes (>99%); PBMS 446/448 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 50, 75 and 100% ethyl acetate in hexanes. Yield 362 **mg**, 86%; HPLC (60/40) 5.06 minutes (97%); mp 227-229.degree. C.; TSPMS 460/462 (MH+, 100%);

DETD (S)-[1-(4-Chloro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (475 **mg**, 1.2 mmol) was dissolved in 4M HCl-dioxane (5 mL) at 0.degree. C. The mixture was stirred for 1.5 hour at 25.degree. C., concentrated and the residue triturated with ether. Yield, 422 **mg**, 105%; TSPMS 283 (MH+, 100%).

DETD . . . Procedure A and the product purified by chromatography on silica gel eluted with 1:1 and 3:1 ethyl acetate/hexanes. Yield 662 **mg**, 69%.

DETD . . . the residue purified by chromatography on silica gel eluted with 5-20% ethanol in dichloromethane containing 0.5% ammonium hydroxide. Yield 232 **mg**, 81%; HPLC (40/60) 2.57 minutes (98%); PBMS 416/418 (MH+, 100%);

DETD (S)-(2-(4-Hydroxy-piperidin-1-yl)-2-oxo-1-[1-(toluene-4-sulfonyl)-1H-imidazol-4-ylmethyl]-ethyl)-carbamic acid tert-butyl ester (512 **mg**, 1.0 mmol) was dissolved in 4 M HCl-dioxane (3 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1.5 hours, concentrated and the residue triturated with ether. Yield, 422 **mg**, 105%; TSPMS 283 (MH+, 100%).

DETD 4-Hydroxypiperidine (303 **mg**, 3.0 mmol), triethylamine (394 **mg**, 3.9 mmol) and diethyl cyanophosphonate (636 **mg**, 3.9 mmol) were added in that order to Boc-N.sub.im -tosyl-L-histidine (J Med Chem 30 536 (1987); 1.32 g, 3.9 mmol). . . . dried and concentrated. The residue was purified by chromatography on silica gel

eluted with 1-8% ethanol in dichloromethane. Yield, 517 **mg**, 35%; HPLC (50/50) 4.75 minutes (97%).

DETD . . . chromatography, along with the more polar serine analog (40%) on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 51 **mg**, 16%; HPLC (60/40) 7.06 minutes (96%); PBMS 348/350 (100%), 543/545 (MH+, <5%).

DETD (S)-[1-Hydroxymethyl-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (595 **mg**, 2.0 mmol) was dissolved in 4M HCl-dioxanes (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 506 **mg**, 105%; MS 189 (MH+, 100%)

DETD . . . extracts were concentrated and the residue purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 751 **mg**, 41%; HPLC (40/60) 2.72 minutes (96%).

DETD . . . dried and concentrated. The residue was purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield, 150 **mg**, 52%; HPLC (60/40) 3.53 minutes (99%); PBMS 442/444 (MH+, 100%);

DETD (S)-[1-(4-Hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (450 **mg**, 1.2 mmol) was dissolved in 4M HCl-dioxane (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1 hour, concentrated and the residue triturated with ether. Yield, 400 **mg**, 107%; MS 265 (MH+, 100%).

DETD . . . foam was purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane containing 0.5% NH.sub.4 OH. Yield 550 **mg**, 41%; HPLC (40/60) 5.02 minutes (87%).

DETD . . . C. reaction temperature) and the product purified by chromatography on silica gel eluted with 1-16% ethanol in dichloromethane. Yield 26 **mg**, 8%; HPLC (50/50) 5.02 minutes (99%); PBMS 427/429 (MH+, 100%);

DETD (S)-[2-(4-Hydroxy-piperidin-1-yl)-2-oxo-1-pyridin-3-ylmethyl-ethyl]-carbamic acid-tert-butyl ester (367 **mg**, 1.05 mmol) was dissolved in 4M HCl-dioxane at 0.degree. C. The resulting suspension was stirred for 1.5 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 450 **mg**, 100%.

DETD . . . acid wash omitted) and the product purified by chromatography on silica gel eluted with 1-8% ethanol in dichloromethane. Yield 454 **mg**, 46%; MS 350 (MH+, 100%).

DETD . . . purified by chromatography on silica gel eluted with 25, 30, 50, 75 and 80% ethyl acetate in hexanes. Yield 150 **mg**, 60%; HPLC (60/40) 3.66 minutes (97%); mp 204-207.degree. C.; PBMS 410 (MH+, 100%);

DETD . . . 0.degree. C. The solution was stirred 2 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 920 **mg**, 124%; HPLC (60/40) 2.23 minutes (98%).

DETD . . . (R)-N-t-Boc-p-fluoro-phenylalanine (3.5 mmol) were coupled according to Procedure A giving a foam which was used without further purification. Yield 940 **mg**, 73%; HPLC (60/40) 3.64 minutes (95%); MS 367 (MH+, 100%).

DETD . . . crude product purified by chromatography on silica gel eluted with 50, 75 and 100% ethyl acetate in hexanes. Yield 171 **mg**, 765%; HPLC (60/40) 4.23 minutes (97%); MS 444/446 (MH+, 100%); TSPMS 444/446 (MH+, 100%);

DETD . . . hexanes. The resulting solid was boiled in ethyl acetate, the resulting suspension filtered, and the collected solid dried. Yield 103 **mg**, 48%; HPLC (60/40) 3.69 minutes (95%); PBMS 428 (MH+, 100%);

DETD . . . the product purified by chromatography on silica gel eluted with 20, 30 and 50% ethyl acetate in hexanes. Yield, 26 **mg**, 8%; HPLC (60/40) 8.14 minutes (98%); PBMS 546/548 (MH+, 100%);

DETD . . . temperature, 1:1 dichloromethane/DMF reaction solvent) and the

product purified by chromatography on silica gel eluted with ethyl acetate. Yield 313 **mg**, 65%; HPLC (60/40) 2.84 minutes (99%); TSPMS 387/389 (MH+, 100%);

DETD . . . The resulting solution was stirred for 2 hours at 25.degree. C., concentrated and the residue triturated with ether. Yield, 390 **mg**, 95%.

DETD . . . 2:1 dichloromethane/dimethylformamide reaction solvent, acid wash omitted, Na.sub.2 SO.sub.4 used for drying). The residue was triturated with ether giving 428 **mg** (86% yield) of a yellow solid.

DETD . . . and 40% ethyl acetate in hexanes. The residue was triturated with 1:1 ether-hexanes, and hexanes giving an off-white solid (484 **mg**, 63%); HPLC (60/40) 8.13 minutes (95%); TSPMS 375/377 (MH+, 100%);

DETD . . . resulting solution was brought to reflux for 1 hour, cooled and concentrated. The residue was triturated with ether. Yield, 515 **mg**, 100%; HPLC (60/40) 2.31 minutes (95%).

DETD . . . was purified by chromatography on silica gel eluted with 10, 20, 30 and 40% ethyl acetate in hexanes. Yield 375 **mg**, 80%; HPLC (60/40) 6.36 minutes (99%); PBMS 392/394 (MH+, 100%);

DETD . . . 25.degree. C. for 2 hours. The mixture was concentrated and the residue triturated with ether giving a yellow solid (321 **mg**, 96%; HPLC (60/40) 2.24 minutes (98%); MS 215 (MH+, 100%).

DETD . . . coupled according to Procedure A (0-25.degree. C. reaction temperature) giving the product which was used without further purification. Yield 426 **mg**, 104%.

DETD . . . eq). After 5 minutes, the reaction mixture was concentrated and the residue triturated with ether giving an orange solid (79 **mg**, 29% yield); TSPMS 385/387 (MH+, 100%);

DETD (S)-[2-(4-Amino-phenyl)-1-dimethylcarbamoyl-ethyl]-carbamic acid tert-butylester (214 **mg**, 0.7 mmol) was dissolved in 4 M HCl-dioxane (2 mL) at 0.degree. C. and the solution stirred for 2 hours at 25.degree. C. The mixture was concentrated and the residue triturated with ether. Yield, 294 **mg**, 102%; PBMS 208 (MH+, 100%).

DETD . . . was purified by chromatography on silica gel eluted with 50, 60, 70 and 100% ethyl acetate in hexanes. Yield 226 **mg**, 42%; HPLC (70/30) 2.45 minutes (100%).

DETD . . . by chromatography on silica gel eluted with 10, 20, 30, 40, 50 and 60% ethyl acetate in hexanes. Yield 263 **mg**, 90%; HPLC (60/40) 7.12 minutes (99%); TSPMS 384/386 (MH+, 100%);

DETD (S)-(1-Dimethylcarbamoyl-3-phenyl-propyl)-carbamic acid tert-butyl ester (235 **mg**, 0.8 mmol) was dissolved in 4 M HCl-dioxane (2 mL) at 0.degree. C. The mixture was stirred at 25.degree. C. for 1.5 hours, concentrated and the residue triturated with ether. Yield, 187 **mg**, 100%; HPLC (60/40) 2.31 minutes (99%).

DETD . . . A (0-25.degree. C. reaction temperature, 3:1 dichloromethane/DMF reaction solvent) giving the product which was used without further purification. Yield 238 **mg**, 93%; HPLC (60/40) 5.98 minutes (97%).

DETD . . . silica gel eluted with 20, 40, 50 and 75% ethyl acetate in hexanes followed by trituration with ether. Yield 400 **mg**, 104%; HPLC (60/40) 3.93 minutes (98%); mp 228-231.degree. C. (dec, yellowed at 210.degree. C.); TSPMS 386/388 (MH+, 100%);

DETD . . . were coupled according to Procedure A. The residue was triturated with ether to give a light yellow solid. Yield, 160 **mg**, 36%; mp 210-213.degree. C. (dec); PBMS 372/374 (MH+, 100%);

DETD [(1S)-(Methoxy carbamoyl)-2-phenyl-ethyl]-carbamic acid tert-butyl ester (200 **mg**, 0.68 mmol) was dissolved in 4 M HCl-dioxane at 0.degree. C. and the mixture stirred at 25.degree. C. After 0.5 . . .

DETD . . . A (0-25.degree. C. reaction temperature). The crude product was triturated with dichloromethane and then with ether and dried. Yield 236 **mg**, 79%; HPLC (60/40) 4.63 minutes (97%); PBMS 356/358 (MH+,

100%);

DETD (R)-(1-Methylcarbamoyl-2-phenyl-ethyl)-carbamic acid tert-butyl ester (722 mg, 2.6 mmol) was dissolved in 4M HCl-dioxane (10 mL) at 0.degree. C. The mixture was stirred for 1 hour at 25.degree. C., concentrated and the residue triturated with ether. Yield, 517 mg, 93%.

DETD . . . hour reaction time, washed with acid first, then base) giving the product which was used without further purification. Yield 760 mg, 96%.

DETD . . . (0-25.degree. C. reaction temperature, 96 hour reaction time). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 24 mg, 96%; HPLC (60/40) 8.05 minutes (97%); PBMS 405/407 (MH+, 100%);

DETD . . . with 6N HCl and extracted with ethyl acetate. The extracts were dried and concentrated giving a light brown solid (458 mg, 34%); HPLC (60/40) 5.31 (93%).

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature) and the resulting foam triturated with 1:1 ether/hexanes and dried. Yield 374 mg, 90%; HPLC (60/40) 6.17 minutes (98%); mp 199-201.degree. C.; PBMS 414/416 (MH+, 100%);

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature). The crude product was triturated with 1:1 ether-hexanes and dried. Yield 302 mg, 87%; HPLC (60/40) 5.46 minutes (99%); mp 198.5-200.degree. C.; PBMS 350 (MH+, 100%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature, 60 hour reaction time) and the resulting foam triturated with ether. Yield 329 mg, 90%; HPLC (60/40) 4.27 minutes (99%); PBMS 366 (MH+, 100%);

DETD . . . to Procedure A (0-25.degree. C. reaction temperature, 60 hour reaction time) and the resulting solid triturated with ether. Yield 320 mg, 91%; HPLC (60/40) 4.74 minutes (100%); mp 229.5-232.degree. C.; PBMS 354 (MH+, 100%);

DETD . . . (0-25.degree. C. reaction temperature) and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate/hexanes. Yield 38 mg, 66%; HPLC (60/40) 4.08 minutes (97%); PBMS 361 (MH+, 100%);

DETD . . . acid (40 mL) and cooled giving a solid which was filtered, washed with cold ethyl acetate and dried: Yield 980 mg 70%; HPLC (60/40) 3.09 minutes (97%).

DETD . . . according to Procedure A (0-25.degree. C. reaction temperature). The resulting solid was triturated with hexanes, then with ether. Yield 272 mg, 81%; HPLC (70/30) 3.49 minutes (99%); mp 199-200.degree. C.; PBMS 336 (MH+, 100%);

DETD . . . hour reaction time) and the crude product purified by column chromatography on silica gel eluted with ethyl acetate. Yield 150 mg, 37%; HPLC (60/40) 3.08 minutes (96%);

DETD (3S,4S)-[1-Benzyl-2-(3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (360 mg, 1.00 mmol) was dissolved in 4 M HCl-dioxane (4 mL) at 25.degree. C. for 3 hours. The mixture was concentrated and the resulting yellow solid triturated with ether and dried. Yield 304 mg, 103%.

DETD Boc-L-phenylalanine (2.2 mmol) and (3S,4S)-dihydroxy-pyrrolidine (U.S. Pat. No. 4,634,775, example 1C, 206 mg, 2.0 mmol) were coupled according to procedure A (0-25.degree. C. reaction temperature) giving a colorless solid which was used without further purification. Yield 431 mg, 61%.

DETD 2(S)-Amino-1-((3RS)-hydroxy-piperidin-1-yl)-3-phenyl-propan-1-one hydrochloride (570 mg, 2.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (429 mg, 2.2 mmol) were coupled according to procedure A (5:2 dichloromethane-dimethylformamide solvent) and the crude product triturated with 1:1 ether-hexanes. The . . . column chromatography on silica gel eluted with 3:2, and 2:1 ethyl acetate/hexanes followed by trituration with 1:1 ether/hexanes. Yield

430 mg, 51%: HPLC (60/40) 3.45 minutes (95%);

DETD 4-((2S)-Amino-3-phenyl-propionyl)-piperazin-2-one hydrochloride (140 mg, 0.5 mmol) and 5-chloro-1H-indole-2-carboxylic acid (98 mg, 0.5 mmol) were coupled according to procedure A and the crude product purified by column chromatography on silica gel eluted with ethyl acetate and 2% ethanol in ethyl acetate followed by trituration with ether. Yield 71 mg, 33%: HPLC (60/40) 3.53 minutes (100%); PBMS 425/427 (MH+, 100%);

DETD [(1S)-Benzyl-2-oxo-2-(3-oxo-piperazin-1-yl)-ethyl]-carbamic acid tert-butyl ester (400 mg, 1.2 mmol) was dissolved in 4M HCl-dioxane (10 ml) at 25.degree. C. for 0.5 hours. The mixture was concentrated and the residue co-evaporated with dichloromethane, trituated with ether, and dried. Yield 340 mg, 103%.

DETD BOC-L-phenylalanine (530 mg, 2 mmol) and piperazin-2-one (J. Am. Chem. Soc. 62 1202 (1940), 200 mg, 2 mmol) were coupled according to procedure A (2:1 dichloromethane/dimethylformamide reaction solvent, washed with 1 N NaOH after acid washes) and the product used without further purification. Yield 404 mg, 58%.

DETD (2S)-Amino-1-morpholin-4-yl-propan-1-one hydrochloride (195 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 mg, 1.0 mmol) were coupled according to procedure A (washed with 1N NaOH after acid washes) giving crude product which was trituated with ether and dried. Yield 150 mg, 45%: HPLC (60/40) 3.61 minutes (100%); PBMS 336/338 (MH+, 100%);

DETD BOC-L-Alanine (3.50 mg, 20 mmol) and morpholine (1.74 g, 20 mmol) were coupled according to procedure A (washed with 1N NaOH after acid. . . .

DETD (2S)-Amino-N-methyl-3-phenyl-propionamide hydrochloride (214 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 mg, 1.0 mmol) were coupled according to procedure A and the crude product trituated with ether and dried. Yield 160 mg, 45%: HPLC (60/40) 4.60 minutes (100%);

DETD BOC-L-phenylalanine (2.65 g, 10 mmol) and methylamine hydrochloride (675 mg, 10 mmol) were coupled according to procedure A (washed with 1N NaOH after acid washes) yielding the title compound as. . . .

DETD (2S)-Amino-N-methoxy-N-methyl-propionamide hydrochloride (169 mg, 1.0 mmol) and 5-chloro-1H-indole-2-carboxylic acid (195 mg, 1.0 mmol) were coupled according to procedure A (washed with 1 N NaOH after acid washes) giving the product (290 mg, 94%): HPLC (60/40) 4.03 minutes (94%); PBMS 310/312 (MH+, 100%);

DETD L-phenylalaninamide hydrochloride (835 mg, 4.17 mmol) and 5-bromo-1H-indole-2-carboxylic acid (1.0 g, 4.17 mmol) were coupled according to procedure A substituting the following workup: the. . . . filtered and the collected solid washed with ethyl acetate, 2 N NaOH, 2 N HCl, ether, and dried. Yield 890 mg; PBMS 386/388 (MH+, 100%);

DETD (2S)-Amino-N-methoxy-N-methyl-3-phenyl-propionamidehydrochloride (317 mg, 1.3 mmol) and 5-chloro-1H-indole-2-carboxylic acid (253 mg, 1.3 mmol) were coupled according to procedure A (0-25.degree. C., washed first with acid, then base). The crude product was. . . . and 40% ethyl acetate in hexanes. The foam obtained was trituated with isopropyl ether yielding an off white solid (356 mg, 71%): HPLC (60/40) 8.28 minutes (98%);

DETD Racemic 2-amino-2-methyl-3-phenyl-propionic acid methyl ester (200 mg, 0.87 mmol) and 5-chloro-1H-indole-2-carboxylic acid (170 mg, 0.87 mmol) were coupled according to Procedure A (2:1 dichloromethane/dimethylformamide solvent) and the product purified by chromatography on silica gel eluted with 10% ethyl acetate in hexanes. Yield 286 mg, 89%: HPLC (60/40) 9.63 minutes (85%); TSPMS 371/373 (MH+, 100%);

DETD Aqueous 2N LiOH (0.10 ml, 0.50 mmol) was added to a solution of (2RS)-[(5-chloro-1H-indole-2-carbonyl)-amino]-2-methyl-3-phenyl-

propionic acid methyl ester (132 mg, 0.36 mmol) in tetrahydrofuran (8 ml) at 25.degree. C. The resulting solution was stirred for 1 hour, concentrated and the. . . organic layer was separated, washed with water, brine and dried giving a foam which was used without further purification (129 mg, 102%): HPLC (60/40) 4.42 minutes (99%); TSPMS 357/359 (MH+, 100%);

DETD m-Chloroperoxybenzoic acid (80 mg of 50%, 0.23 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiomorpholin-4-yl-ethyl)-amide (100 mg, 0.23 mmol) in dichloromethane (2 mL). After 1 hour, the mixture diluted with ethyl acetate and washed three times with. . .

DETD m-Chloroperoxybenzoic acid (202 mg of 50%, 0.58 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiomorpholin-4-yl-ethyl)-amide (100 mg, 0.23 mmol) in dichloromethane (2 mL). After 1 hour, the mixture was diluted with ethyl acetate and the resulting solution. . .

DETD m-Chloroperoxybenzoic acid (167 mg of 50%, 0.48 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid ((1S)-benzyl-2-oxo-2-thiazolidin-3-yl-ethyl)-amide (200 mg, 0.48 mmol) in dichloromethane (4 mL). After 0.5 hours, the mixture was diluted with ethyl acetate and washed three times. . . on silica gel eluted with 1-8% ethanol in dichloromethane and then triturated with ether giving the title compound. Yield 151 mg (73%); HPLC (60/40) 3.64 minutes (98%); PBMS 430/432 (MH+, 100%);

DETD Hydroxylamine hydrochloride (68 mg, 0.82 mmol) and potassium carbonate (136 mg, 0.98 mmol) were added to a solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-oxo-2-(3-oxo-pyrrolidin-1-yl)-ethyl]-amide in ethanol (5 ml) and water (1 ml) at. .

DETD Yield 48 mg (14%); HPLC (60/40) 4.69 minutes (97%); mp 216-220.degree. C. (darkened at 210.degree. C.); PBMS 425/427 (MH+, 100%).

DETD Yield 69 mg (20%); HPLC (60/40) 6.78 minutes (>99%); mp 223-224.degree. C. (dec, tar); PBMS 425/427 (MH+, 100%);

DETD . . . 30%, 40%, 50%, 75% and 100% ethyl acetate in hexane giving partial separation. The pure fractions were pooled giving 31 mg (25%) of the title substance: HPLC (60/40) 9.38 minutes (94%); PBMS 410/412 (MH+, 100%);

DETD [(5-Chloro-1H-indole-2-carbonyl)-amino]-acetic acid methyl ester (100 mg, 0.40 mmol) was added to a saturated solution of ammonia in methanol (ca. 3 mL) at 25.degree. C. The suspension. . . was sonicated for 1 hour and the resulting solution concentrated. The residue was triturated with ether/hexanes and dried. Yield 77 mg, 77%; HPLC (60/40) 2.78 minutes (98%); PBMS 252/254 (MH+, 100%);

DETD Trifluoroacetic acid was added to a solution of 1-((2S)-[(5-bromo-1H-indole-2-carbonyl)-amino]-3-phenyl-propionyl)-pyrrolidine-(2S)-carboxylic acid tert-butyl ester (345 mg, 0.64 mmol) in dichloromethane (2 ml) at 0.degree. C. After 1 hour at 25.degree. C., the reaction mixture was concentrated, triturated with ether and dried giving a yellow solid. Yield 273 mg, 88%; HPLC (70/30) 4.75 minutes (98%); TSPMS 484/486 (MH+, 100%);

DETD L-phenylalanine-L-proline tert-butyl ester (333 mg, 1.0 mmol) and 5-bromo-1H-indole-2-carboxylic acid were coupled according to procedure A (72 hour reaction time). The product was purified by. . . column chromatography on silica gel eluted with 15%, 20% and 30% ethyl acetate giving a pale yellow foam. Yield 428 mg (79%); HPLC (70/30) 5.84 minutes (81%).

DETD m-Chloroperoxybenzoic acid (426 mg of 50%, 1.2 mmol) was added at 25.degree. C. to a solution of 5-chloro-1H-indole-2-carboxylic acid (2-oxo-2-thiazolidin-3-yl-ethyl)-amide (400 mg, 1.2 mmol) in dichloromethane (8 mL) at 25.degree. C. After 1 hour, the mixture was diluted with ethyl acetate (ca. . .

DETD Excess aqueous 2 M LiOH was added to a solution of 1-[(2S)-[(5-chloro-1H-indole-2-carbonyl)-amino]-3-phenyl-propionyl)-(4R)-hydroxy-pyrrolidine-(2S)-carboxylic acid benzyl ester (215 mg, 0.40 mmol) in tetrahydrofuran at 25.degree. C. After 2 hours, the mixture was diluted with ethyl acetate and ice and . . . and the organic layers combined and dried. The residue was triturated with ether and dried giving a colorless solid (190 mg, 106%): HPLC (60/40) 3.43 minutes (94%); TSPMS 456/458 (MH+, 100%);

DETD A solution of 3-[(5-chloro-1H-indole-2-carbonyl)-amino]-acetyl)-thiazolidine-2-carboxylic acid methyl ester (196 mg, 0.5 mmol) in methanol (10 mL) was treated with aqueous 1 N NaOH (0.5 mL) at 25.degree. C. After 3. . . organic layers were combined, dried, and concentrated giving a solid which was triturated with 1:1 ether-hexane and dried. Yield 186 mg, 99%; HPLC (60/40) 3.13 minutes (98%); TSPMS 368/370 (MH+, 70%), 339 (100%).

DETD . . . silica gel eluted with 25%, 50%, 75% and 100% ethyl acetate-hexanes giving the title substance as a colorless foam (104 mg, 22%). A mixture (180 mg) of less polar products was also isolated. Title substance: HPLC (60/40) 4.18 minutes (97%); TSPMS 398/400 (MH+, 100%);

DETD [(1S)-Benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (515 mg, 1.6 mmol) was dissolved in cold 4N HCl-dioxane, the mixture stirred 2 h at 25.degree. C., concentrated, and the residue coevaporated with ether giving a colorless solid (415 mg, 100%).

DETD A solution of 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-oxo-azetidin-1-yl)-2-oxo-ethyl]-amide (product of Example 170, 50 mg, 0.13 mmol), sodium acetate trihydrate (43 mg, 0.32 mmol) and hydroxylamine hydrochloride (18 mg, 0.25 mmol) in methanol (2 mL) was heated at reflux for 8 h and concentrated. The residue was partitioned between. . . The organic layer was separated and dried giving a colorless solid which was triturated with ether-hexanes and dried (yield 36 mg, 69%): HPLC (50/50) 6.74 min (99%); TSPMS 411/413 (MH+, 10%), 180 (100%); .sup.1 H NMR (DMSO-d.sub.6) .delta. 11.75 (br, 1H), . . .

DETD A mixture of 5-chloro-1H-indole-2-carboxylic acid [1(S)-benzyl-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl]-amide (406 mg, 0.96 mmol), hydroxylamine hydrochloride (80 mg, 1.15 mmol), and potassium carbonate, (159 mg, 1.15 mmol) in ethanol (6 mL) and water (1 mL) was stirred at 25.degree. C. for 18 h and concentrated. The residue was dissolved in ethyl acetate and the resulting solution washed with water and dried (411 mg, 98%): HPLC (60/40) 5.13 minutes (97%); TSPMS 439/441 (MH+, 100%);

DETD 5-Chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide (Example 46, 669 mg) was added in one portion at 0.degree. C. to a mixture of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC, 1.80 g, 9.4 mmol) and dichloroacetic acid (307 mg, 1.5 mmol) in anhydrous toluene (e mL) and anhydrous dimethylsulfoxide (e mL). The mixture was stirred at 0-20.degree. C. for. . . the residue purified by chromatography on silica gel eluted with 25%, 50%, and 75% ethyl acetate-hexanes giving a foam (424 mg, 64%).

DETD [(1S)-Benzyl-2-(1,3-dihydro-isoindol-2-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (88 mg) was dissolved in cold 4N HCl-dioxane (1.5 mL), stirred 2 h at 25.degree. C., and the mixture concentrated. The residue was triturated with ether and dried (65 mg, 91%). TSPMS 267 (MH+, 100%).

DETD . . . the product purified by chromatography on silica gel eluted with 20% and 50% ethyl acetate-hexanes giving an amber oil (88 mg, 23%): TSPMS 367 (MH+, 100%).

DETD . . . eluted with 20%, 30%, 40% and 50% ethyl acetate in hexane giving the title substance as a colorless foam (600 mg, 47%):

HPLC (60/40) 5.09 minutes (98%); TSP-MS 396 (MH+, 100%); 1H NMR (CDCl₃.sub.3) .delta. 9.14 (br, 1H), 7.62 (d, 1H, . . .

DETD [(1S)-Benzyl-2-oxo-2-(3-oxo-azetidin-1-yl)-ethyl]-carbamic acid tert-butyl ester (297 mg, 0.9 mmol) was dissolved in 4N HCl-dioxane (3 mL). The resulting solution was stirred at 25.degree. C. for 2 h, concentrated, and the residue triturated with ether and dried (196 mg, 82%).

DETD [(1S)-Benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (320 mg, 1 mmol) was added in one portion to a mixture of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (DEC, 575 mg, 3 mmol) and dichloroacetic acid (192 mg, 1.5 mmol) in anhydrous toluene (2 mL) and anhydrous dimethylsulfoxide (2 mL). The mixture was stirred at 0-20.degree. C. for . . . solution washed twice with 1 N HCl, twice with saturated aqueous NaHCO₃, dried and concentrated giving a colorless solid (304 mg, 96%).

DETD . . . coupled according to Procedure A and the product purified by chromatography on silica gel eluted with 1:1 ethyl acetate-hexanes (235 mg, 63%): HPLC (60/40) 4.92 min (91%); PBMS 371/373 (MH+, 100%); .sup.1 H NMR (CDCl₃.sub.3) .delta. 11.25 (br, 0.6H), 10.9 (br, . . .

DETD . . . were coupled according to Procedure A (3:1 dimethylformamide-dichloromethane reaction solvent) and the product triturated with 2:1 ether-hexanes and dried (130 mg, 63%): HPLC (60/40) 6.22 minutes (95%); TSPMS 429/431 (45%, MH+NH₃), 412/414 (30%, MH+), 325/327 (100%). .sup.1 H NMR (DMSO-d₆) .delta. . . .

CLM What is claimed is:
36. The method as recited in claim 34 for treating **diabetes** in a mammal by administering to a mammal suffering from **diabetes** a **diabetes** treating amount of a compound of claim 1.

L8 ANSWER 3 OF 3 USPATFULL

TI Complexed **vanadium** for the treatment of **diabetes** mellitus

PI US 5300496 19940405 <--

SUMM **Diabetes** is a mammalian condition in which the amount of glucose in the blood plasma is abnormally high. The condition can be life-threatening and high glucose levels in the blood plasma (hyperglycemia) can lead to a number of chronic **diabetes** syndromes, for example, atherosclerosis, microangiopathy, kidney disorders, renal failure, cardiac disease, diabetic retinopathy and other ocular disorders including blindness.

SUMM . . . automatically in a complex procedure that involves, inter alia, the hormone insulin. In diabetics, external intervention is needed. Treatment of **diabetes** is now carried out using several drugs. Insulin is the mainstay of treatment; it replaces the natural hormone produced in the pancreas. In **diabetes**, insulin is not produced in sufficient quantities, or the body becomes resistant to insulin and requires more than normal amounts. . . .

SUMM Oral **diabetes** medications are available. **Sulfonylureas** depend on insulin release in the body and are therefore not effective in patients who cannot make their own insulin.. . .

SUMM . . . by Cantley and co-workers to be a potent inhibitor of Na.sup.+ -K.sup.+ ATPase (1). The same group showed that vanadate (**vanadium**+5) taken up by the red blood cells was reduced to **vanadium** +4 in the form of vanadyl ion V=O.sup.2+ in the cytoplasm (2).

SUMM Since the above work, there has been a significant focus on the effects of **vanadium**, mostly as vanadate, on glucose metabolism and uptake into cells. A natural outgrowth of this work has been the study of **vanadium** and **diabetes** (3).

SUMM . . . vanadyl sulfate will also lower blood glucose and blood lipids in STZ diabetic rats and will prevent secondary complications of

diabetes such as cataracts and cardiac dysfunction. Vanadyl sulfate is less toxic than the vanadate form of **vanadium** but is also poorly absorbed. There have only been two attempts to modify the biological uptake of **vanadium** by changing the chemical form in which it is supplied from either vanadate (VO.sub.4.sup.3-) or vanadyl sulfate (VOSO.sub.4.(H.sub.2 O).sub.x), which has been used because the active form of **vanadium** may be the vanadyl ion. Work on **vanadium** peroxides has been carried out by Posner et al. (12,13) and U.S. Pat. No. 4,882,171 to Fantus and Posner was issued on Nov. 21, 1989. It relates to **vanadium**-peroxide compositions as insulin mimics. This work involves in vitro studies of co-administered vanadate and peroxide.

- SUMM . . . issued Mar. 1, 1989 to Lazaro et al. describes and claims a vanadyl cysteine compound for the oral treatment of **diabetes**. The compound in the European patent has the structure: ##STR1##
- SUMM There is a need for medication, preferably to be taken orally, that is effective in the treatment of **diabetes**. Accordingly, the present invention provides a pharmaceutical composition useful for lowering blood sugar and depressing appetite in a mammal, the composition comprising a **vanadium** compound of the formula:
- SUMM Preferably, the **vanadium** compound has a structure selected from: ##STR3## in which R is as defined above and R.sub.1 is the balance of.
- SUMM . . . present invention is also a method of lowering blood sugar in a mammal that comprises administering to the mammal a **vanadium** compound of the general formula:
- DETD . . . pharmacological effectiveness of the compound. Using male rats, made diabetic by the injection of STZ at a dose of 60 mg/kg i.v., the compound was initially given by intraperitoneal (i.p.) injection as a suspension in 1% methyl cellulose.
- DETD Nine out of the twelve rats given 15 mg/kg i.p. (0.05 mmol/kg) responded to the compound with a decrease in blood glucose. Two animals developed hypoglycemia.
- DETD a. Drinking. Administration of the vanadyl compound in the drinking water at doses of 0.46-0.92 mmol/kg (150-300 mg/kg, using concentrations of 0.5-1.3 mg/mL) reduced blood glucose in four diabetic rats into the normal range. Fluid intake was also decreased to normal in these. . .
- DETD . . . Control-Treated (11 animals), Diabetic (11 animals) and Diabetic-Treated (12 animals). The diabetic state was induced by injecting STZ at 60 mg/kg dissolved in 0.9% NaCl I.V. via the tail vein to anaesthetised rats. The two control groups were injected with 0.9%. . .
- DETD . . . began with a 3.17 mM solution of the compound. On day 6, the concentration was reduced to 1.58 mM (0.5 mg/mL). On day 24, the concentration was increased to 2.37 mM (0.7 mg/mL). At this point 8 out of the 12 animals were responding to the compound.
- DETD The present invention provides a pharmaceutical composition useful for the treatment of **diabetes** mellitus, or an appetite suppressant, or both. The active compounds are absorbed across the gastrointestinal barrier and deliver the vanadyl ion to the bloodstream, where the insulin-mimetic properties of **vanadium** can be expressed. In contrast to insulin, the compositions are active when taken by mouth, and represent a significant advance in **diabetes** therapy. The compositions are also useful as orally active appetite suppressants and would be effective in treating obesity. The majority.
- DETD 2. Cantley, L.C. Jr. and Aisen, P. "The fate of cytoplasmic **vanadium** implications on (Na,K)-ATPase inhibition." J. Biol. chem. 254:1781-1784, 1979.
- DETD 3. Reviewed in Shechter, Y. "Insulin-mimetic effects of vanadate: possible implications for future treatment of **diabetes** "

Diabetes 39:1-5, 1990.

DETD . . . "Detection of oxovanadium(IV) and characterization of its ligand environment in subcellular fractions of the liver of rats treated with pentavalent **vanadium(V)**." Biochem. Biophys. Res. Comm. 96:293-298, 1980.

DETD 7. Ramanadham, S., Mongold, J.J., Brownsey, R.W., Cros, G.H. and McNeill, J.H. "Oral vanadyl sulfate in treatment of **diabetes** mellitus in rats". Amer. J. Physiol. 257:H904-H911, 1989.

DETD 9. Pederson, R.A., Ramanadham, S., Buchan, A.M.J. and McNeill, J. "Long term effects of vanadyl treatment on streptozotocin-induced **diabetes** in rats". **Diabetes** 38(11):1390-1395, 1989.

DETD 11. Ramanadham, S., Heyliger, C., Gresser, M.J. Tracey, A.S. and McNeill, J.H. "The distribution and half-life for retention of **vanadium** in the organs of normal and diabetic rats orally fed **vanadium(IV)** and **vanadium(V)**." Biol. Trace Elements (in press) 1991.

DETD 12. Kadota, S. et al. "Peroxide(s) of **vanadium** a novel and potent insulin-mimetic agent which activates the insulin receptor kinase" Biochem. Biophys. Res. Comm. 147:259-266, 1987.

DETD 17. Jungnickel, J.E. and Klinger, W. "Photometrische bestimmung von **vanadium** mit 2-methyl-3-hydroxy- -pyron(maltol)." Z. Anal. Chem. 203:257-260, 1964.

CLM What is claimed is:

. . . method as claimed in claim 1 in which the bis(maltotao)oxovanadium(IV) is administered by injection at a dose of about 15 mg/kg.

. . . as claimed in claim 4 in which the bis(maltolato)oxovanadium(IV) is administered orally at a dose in the range of 150-300 mg/kg.